

**BIOGRAPHICAL SKETCH**

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NAME: Chen, Lizhen

eRA COMMONS USER NAME (credential, e.g., agency login): LIZHEN\_CHEN

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Lanzhou University, China	B.S	07/2000	Biochemistry
University of Georgia	Ph.D	12/2008	Genetics
University of California, San Diego	Postdoc	03/2016	Genetics & Neurobiology

**A. Personal Statement**

The goal of my research is to discover molecular pathways involved in neuronal aging and disease, and to translate such findings into potential therapeutic targets. I have over 16 years of experience in molecular and genetic analyses in two model organisms, mouse and *C.elegans*. I worked as a lab tech after graduating from college and studied neural development and neuron apoptosis in Nanjing University. My graduate work at University of Georgia was to understand the transcriptional regulation of thymus organ development, aging and evolution, primarily using mouse model. My postdoc training started from a genetic screen for factors regulating axon regeneration after injury. I then focused on mechanistic studies of two players identified from the screen, one is a microtubule regulator EFA6 and the other is an RNA binding protein CELF. The connection between CELF2 and age-associated neurodegeneration leads me to hypothesize that CELF2 plays a critical role in Alzheimer's disease (AD) and can be a potential therapeutic target. I started my own laboratory in May 2016 in the University of Texas Health Science Center San Antonio (UTHSCSA). I am taking advantage of insights, technologies and reagents from my postdoc work to study the role of CELF2 RBP in neuronal aging and age-associated neurodegeneration, particularly in AD. I have supervised over 10 undergrads, rotation students and postdoctoral fellows in the past 10 years. This mentoring experience and my expertise in mouse genetics, cellular biology and neurobiology make me a qualified mentor in the Xiangya Medical Student Research Program.

1. **Chen L**, Liu Z, Zhou B, Wei C, Zhou Y, Rosenfeld M, Fu X, Chisholm A and Jin Y (2016) CELF RNA binding proteins promote axon regeneration in *C. elegans* and mammals through alternative splicing of syntaxins. *eLife*.16072. PMID: 27253061
2. **Chen L**, Chuang M, Koorman T, Boxem M, Chisholm A and Jin Y (2015) Axon injury triggers EFA-6 mediated destabilization of axonal microtubules via TACC and doublecortin like kinase. *eLife*.08695. PMID: 26339988
3. **Chen L**, Wang Z, Hubert T, Ghosh-Roy A, O' Rourke S, Bowerman B, Wu Z, Jin Y, Chisholm A. (2011) Axon regeneration pathways identified by systematic genetic screening in *C. elegans*. *Neuron* 71(6):1043-57 PMID: 21943602
4. **Chen L**, Gao X. Neuronal apoptosis induced by endoplasmic reticulum stress. (2002) *Neurochem Res*. 27(9):891-8 PMID: 12396099

## B. Positions and Honors

### Positions and Employment

2016-Current : Assistant Professor, Barshop Institute, Department of Cell Systems and Anatomy, University of Texas Health Science Center, San Antonio  
2009-2016: Postdoctoral Scholar, HHMI, University of California, San Diego  
2003-2008: Ph.D student, Genetics Department, University of Georgia  
2000-2003: Research assistant and lab manager, Nanjing University

### Other Experience and Professional Memberships

#### *Membership*

2009-Current: Member of Genetics Society of America  
2003-2008: Member of Society of Developmental Biology

#### *Ad Hoc Reviewer*

2010- Journal reviewer for: *Life Science Research, Science China, Genetics and Epigenetics, Journal of Central Nervous system Disease.*

#### *Mentoring (2007 – 2016):*

Postdoc fellow: Aiping Xu, UTHSCSA (Mentor)  
Undergraduate student: Cristina Duran (Mentor)  
Postdoc fellow: Hanzhou Wang, UTHSCSA (Co-mentor)  
Postdoc fellow: Mingjun Bi, UTHSCA (Co-mentor)  
Postdoc fellow: Xue Li, UTHSCSA (Co-Mentor)  
Rotation graduate student: Mignon Chu, UC San Diego  
Rotation graduate student: Marian Chuang, UC San Diego  
Rotation graduate student: Hannah Al-Sodani, UC San Diego  
Rotation graduate student: Yiren Hu, UC San Diego  
Rotation graduate student: Victory Joseph, UC San Diego  
Undergraduate student: Laura Toy, UC San Diego  
Rotation graduate student: Heidi Roberson, Univ of Georgia  
Undergraduate student: Brian Le, University of Georgia  
Undergraduate student: Jeff Raptor, University of Georgia

### Honors

01/2014: 1000 Talent Plan Award, the Chinese Recruitment Program of Global Youth Experts  
12/2007: Graduate Travel Award, University of Georgia  
2005-2007: Graduate Travel Award, Genetics Department, University of Georgia  
06/2000: Graduation with Distinction, Lanzhou University, Lanzhou, China  
1996-2000: Undergraduate Scholarship, Lanzhou University, Lanzhou, China

## C. Contribution to Science

**1. Neuronal function of CELF RNA binding protein.** I have investigated the role of a conserved RNA binding protein (RBP) UNC-75/CELF in promoting axon regeneration. Using genomic approaches, I found CELF is a key regulator of genes involved in membrane trafficking and neurotransmission by regulating alternative splicing and mRNA stability. In addition, by generating a conditional knockout allele of Celf2 in mouse, I have shown that CELF RBP function in axon regeneration and alternative splicing of syntaxin genes is conserved cross species.

- a. **Chen L**, Liu Z, Zhou B, Wei C, Zhou Y, Rosenfeld M, Fu X, Chisholm A and Jin Y (2016) CELF RNA binding proteins promote axon regeneration in *C. elegans* and mammals through alternative splicing of syntaxins. *eLife*.16072. PMID: 27253061

2. **Axonal microtubule regulation.** My previous work has linked EFA-6, a novel intrinsic inhibitor of adult axon regeneration, to microtubule regulators TACC and DCLK. I revealed that EFA-6 responds to axon injury and changes cellular localization, and this injury response is critical for its function in controlling microtubule dynamics and axon regeneration. EFA-6 is known as a GEF for ARF-6 GTPase. However I have demonstrated that EFA-6 function is independent of GEF activity, but dependent on its N-terminus instead. Genetic interaction and cell biological analyses showed that EFA-6 functions through regulating microtubule dynamics. By imaging GFP tagged microtubule plus end binding protein, I have shown that EFA-6 negatively regulates microtubule growth, a process critical for axon regrowth after injury.
  - a. **Chen L**, Chuang M, Koorman T, Boxem M, Chisholm A and Jin Y (2015) Axon injury triggers EFA-6 mediated destabilization of axonal microtubules via TACC and doublecortin like kinase. *eLife*.08695. PMID: 26339988
3. **Molecular mechanisms of axon regeneration.** My postdoc work has greatly advanced our understanding in molecular mechanisms underlying axon regeneration by identifying novel regulators. I carried out a genetic screen for genes involved in axon regeneration using *C. elegans* and screened over 600 conserved genes. I have identified both regeneration-promoting genes and regeneration-inhibiting genes. These genes encode proteins in different functional groups, suggesting that axon regeneration requires crosstalk of different pathways. Many of these genes had not previously been implicated in regulating axon regeneration. My screen provided the first glimpse of the broader genetic landscape of axon regeneration. I have further carried out mechanistic studies to understand the roles of those identified genes, linking those newly identified genes to previously known pathways involved in axon regeneration
  - a. **Chen L**, Liu Z, Zhou B, Wei C, Zhou Y, Rosenfeld M, Fu X, Chisholm A and Jin Y (2016) CELF RNA binding proteins promote axon regeneration in *C. elegans* and mammals through alternative splicing of syntaxins. *eLife*.16072. PMID: 27253061
  - b. **Chen L**, Wang Z, Hubert T, Ghosh-Roy A, O' Rourke S, Bowerman B, Wu Z, Jin Y, Chisholm A. (2011) Axon regeneration pathways identified by systematic genetic screening in *C. elegans*. *Neuron* 71(6):1043-57 PMID: 21943602
  - c. **Chen L** and Chisholm A. (2011) Axon regeneration mechanisms: insights from *C.elegans*. *Trends in Cell Biology* 21(10):577-84 PMID: 21907582
4. **Transcriptional regulation in thymus development, aging and evolution.** My graduate work addressed important questions in thymus development, aging and evolution. I have shown that the dosage of Foxn1 is critical for its function. In addition, my data provide the first functional evidence that Foxn1, a Forkhead box family transcription factor, is required for the homeostasis of thymic epithelial cells in adult thymus in a dosage-specific manner. My results also show that changing the expression of a single TEC-specific gene can recapitulate all aspects of thymic involution. I also carried out the first precise cross-species gene swap using gene targeting in mouse to study the evolution of HOXA3 protein, which plays important role in thymus development and evolution. My data provide evidence that the zebrafish Hoxa3a and mouse Hoxa3 proteins have functionally diverged since their last common ancestor, due to changes outside the homeodomain, significantly moving forward our understanding of the functional evolution of Hox genes.
  - a. **Chen L**, Zhao P, Wells L, Amemiya C, Condie B, Manley N. (2010) Mouse and zebrafish Hoxa3 orthologs have non-equivalent *in vivo* protein function. *PNAS* vol. 107 no. 23 10555-10560 PMID: 20498049
  - b. **Chen L**, Xiao S, Manley N. (2009) Foxn1 is required to maintain the postnatal thymic microenvironment in a dosage-sensitive manner. *Blood*. 113(3):567-74 PMID: 18978204

#### Complete List of Published Work in MyBibliography:

[https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/?reload=addfrompubmed&sortby=date&groupby=citation\\_type](https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/?reload=addfrompubmed&sortby=date&groupby=citation_type)

#### D. Research Support

Ongoing research support

UTHSCSA Start-Up Fund Role: PI

05/01/2016 – 04/31/2021

Women Health Pilot Grant, School of Medicine, UTHSCSA    Role: Co-PI    08/01/2016 – 07/31/2017

Pending research support

NIH RFA-GM-17-004 “Maximizing Investigators Research Award for Early Stage Investigators (R35)”  
Role: PI    07/01/2017 – 06/30/2022

AFAR Research Grant for Junior Faculty    Role: PI    07/01/2017 – 06/30/2019

AFAR The New Investigator Awards in Alzheimer's Disease    Role: PI    07/01/2017 – 06/30/2019

Nathan Shock Pilot Grant    Role: PI    07/01/2017 – 06/30/2018

Completed research support

NIH T32 AG00216-2 (Neuroplasticity of Aging)    Role: PI    05/01/2013 – 04/30/2014

## Summary of the project that Xiangya students would be participating (Lizhen Chen's Lab)

### Exploring the roles of the GWAS risk factor CELF2 in Alzheimer's Disease

Neuronal aging is the greatest risk factor for age-associated neurodegenerative disorder including Alzheimer's disease (AD). A previous genome-wide association study (GWAS) of multiplex late-onset AD families has revealed the single nucleotide polymorphisms (SNPs) of CELF2 associated with AD. CELF2 encodes an RNA binding protein (RBP) a member of the conserved CELF (CUGBP and Elav like) family RBP. Changes in CELF2 expression have been found in patients and animal models with neuronal injury or degenerative diseases. Management of CELF2 expression was able to attenuate some of the pathological changes. We have generated *Celf2* conditional knockout allele and our preliminary studies show that neuron-specific knockout of *Celf2* knockout mice displayed abnormal development and behavior. Using CLIP-seq (cross-linking immunoprecipitation high-throughput sequencing) we have identified mRNA targets of mouse CELF2 and found that CELF2 binds to mRNAs of AD associated genes, including APP, PSEN1, PSEN2 and MAPT. Our preliminary data also show that alternative splicing of exon 10 is altered in the brain of *celf2* knockout mice. There is evidence that dysregulation of Tau exon 10 alternative splicing is sufficient to cause neurodegeneration. Therefore we propose the following specific aims to test hypotheses related to the role of CELF2 in AD.

**Aim 1: To test the hypothesis that CELF2 expression is altered in the brain with aging and in AD models.** Previous studies have shown changes in CELF2 expression in various neurodegeneration rodent models and human patients. However the data are controversial to some extent, with CELF2 up-regulated in some models and down regulated in others. We will investigate CELF2 expression at both protein and mRNA levels in different brain compartments during normal aging and in AD mouse models. The subcellular localization of RBPs is critical for their functions, so we will also determine the subcellular localization of CELF2 at different stages with confocal microscopy.

**Aim 2: To test the hypothesis that changes in CELF2 expression contributes to age-associated neurodegeneration and that manipulating CELF2 expression will attenuate neurodegeneration.** We will first use a culture AD model to test whether changing CELF2 expression will affect AD-like pathology. Although it's not feasible to be completed within the pilot grant period, *in vivo* studies will be performed following the *in vitro* tests. We have generated a *Celf2* conditional knockout allele. *Celf2* whole-body knockout is neonatal lethal, suggesting its essential role in development. We will cross *Celf2* cKO allele to 3xTg AD mouse and use tamoxifen induced Cre to knockout *Celf2* at specific time points to test whether loss of CELF2 affects neuropathology in AD model animals. We will also use adeno-associated virus (AAV) to express CELF2 and examine the effect of elevating CELF2 expression in AD mice.

**Aim 3: To explore the molecular mechanisms by which CELF2 is involved in AD.** We have performed CELF2 CLIP-seq and identified genome-wide mRNA targets. Our data suggest that CELF2 regulates alternative splicing via binding to introns, as well as control mRNA stability and translation of many important neuronal genes via binding to their 3' ends. We will perform bioinformatics analyses on CELF2 targets followed by functional tests on candidate targets. Targets that have been linked to or implicated in neurodegeneration (e.g. Tau) will be analyzed for their regulation by CELF2 and their roles in AD.

The Xiangya student will be participating in the project under my direct supervision. Support from the Xiangya Program will allow us to start to understand the roles of CELF2 in the brain during aging, characterize novel *celf2* cKO mouse models of interest to the AD and neurodegeneration field, to test whether expression of CELF2 can be used as a biomarker to monitor disease onset and progression and whether manipulating CELF2 expression provides a novel strategy for disease intervention, and to establish the functional connections with other biological pathways and pathogenic mechanisms. Data obtained from the study will provide basis for our next-step investigations and will support our external funding application. We expect to publish at least one paper with the Xiangya student as the first author before the Xiangya student graduates.